ST. MARY'S HOSPITAL, THE CATHOLIC UNIVERSITY OF KOREA

Aplastic Anemia in a Petrochemical Factory Worker

Young Mann Baak, Byoung Yong Ahn, Hwang Shin Chang, Ji Hong Kim, Kyoung Ah Kim, and Young Lim

Department of Industrial Medicine, St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

A petrochemical worker with aplastic anemia was referred to our hospital. He worked in a petroleum resin-producing factory and had been exposed to low-level benzene while packaging the powder resin and pouring lime into a deactivation tank. According to the yearly environmental survey of the working area, the airborne benzene level was approximately 0.28 ppm. Exposure to benzene, a common chemical used widely in industry, may progressively lead to pancytopenia, aplastic anemia, and leukemia. The hematotoxicity of benzene is related to the amount and duration of exposure. Most risk predictions for benzene exposures have been based on rubber workers who were exposed to high concentrations. In the petroleum industry, the concentration of benzene is relatively low, and there are disputes over the toxicity of low-level benzene because of a lack of evidence. In this paper we report the case of aplastic anemia induced by low-level benzene exposure. *Key words:* aplastic anemia, benzene, petrochemical worker. *Environ Health Perspect* 107:851–853 (1999). [Online 13 September 1999]
http://ehpnet1.niehs.nih.gov/docs/1999/107p851-853baak/abstract.html

Case Presentation

A 45-year-old petrochemical worker with aplastic anemia was referred to our department of industrial medicine in November 1998 to evaluate a relationship between his job history and the disease. The patient worked in a petroleum resin-producing factory that used heavy raw pyrolysis gasoline (H-RPG) containing 0.3% benzene as a raw material. The petroleum resins are used primarily in the production of paints and adhesives.

In 1977 the patient began working in a packaging-process area where he packed powder resin into bags. Each bag weighed 80 kg, and the patient normally worked 8 hr/day. In May 1993 he moved to a deactivation-process area where he poured lime into a deactivation tank twice a day, 40 kg each time, and drained the tank after the chemical reaction (Figure 1). The patient actually spent < 30 min/day in the deactivation process; for the remainder of the work day, he waited in a control room. Other than doing routine work in the packaging and deactivation processes, he also occasionally cleaned the reaction tank; because of this the patient may have been exposed to high-level benzene for short periods. While working he wore a facial mask for protection from resin powder and noxious gas.

In September 1998 the patient complained of fatigue and lethargy. He visited a local clinic and routine physical and laboratory examinations were performed. The blood test performed at this time showed pancytopenia and the patient was referred to St. Mary's Hospital. After admission to the department of hematology, a bone marrow biopsy was performed. This biopsy showed hypocellularity with fatty infiltration, which is consistent with aplastic anemia. A chromosomal study showed a normal male karyotype without any aberrations.

The patient did not smoke cigarettes or drink alcoholic beverages, and his history of drug and radiation exposure was insignificant. His serologic markers and history of viral infection were negative. There were no abnormal hematologic findings in the patients's yearly occupational fitness examination at the factory, which was taken before the onset of his symptoms (Table 1).

Because there was no matching compatible donor, the patient was given blood transfusions, antilymphocyte immunoglobulins, and cyclosporin. He was discharged in December 1998 with symptomatic improvement and laboratory stabilization. In January 1999, he was readmitted and treated for opportunistic herpes zoster infection.

Industrial hygienists performed routine environmental surveys of the factory twice each year from 1993 to 1998; the air concentrations of benzene were approximately 0.28 ppm. We performed an environmental survey of the workplace again after the patient was referred (Table 2). We also measured *trans-trans*-muconic acid (tt-MA) in the urine of workers to assess benzene exposure.

Discussion

Benzene, an aromatic hydrocarbon, is used widely in industries as a solvent for rubber and inks and as a starting material in chemical synthesis. It is a natural constituent of petroleum, and the general population is exposed to benzene from gasoline, indoor air, smoking, car exhaust, and groundwater. The hematotoxicity of benzene is related to the amount and duration of exposure (*1*). At high levels of exposure (air concentration > 100 ppm), the incidence of aplastic anemia is approximately 1/100 individuals exposed; at lower levels of exposure (10–20 ppm), this drops abruptly to approximately 1/10,000 (*2*). In the past, benzene exposure > 100 ppm frequently occurred in workplaces, and the causal relationship between high-level benzene exposure and its toxicity has been known since the nineteenth century. As data indicating carcinogenecity of benzene increased (*3,4*), the standards of occupational exposure and the airborne level in workplaces have been progressively lowered. In Korea, benzene levels in paint production, printing, and glue adhesion are approximately 2.0 ppm [geometrical mean (*5*)]; in the petroleum industry in the United States, the level of benzene is 0.3 ppm for an 8-hr time-weighted average (TWA) (*6*).

Risk assessment studies have demonstrated that there is significant excess risk associated with a lifetime exposure to 10 ppm benzene and that this risk would be lowered with a decrease in the exposure level. In 1987, the U.S. government lowered the

Address correspondence to Y. Lim, Department of Industrial Medicine, St. Mary's Hospital, The Catholic University of Korea, 62 Youido-dong, Youngdungpo-gu, Seoul, 150-010, Korea. Telephone: 82 02 3779 1401. Fax: 82 02 782 6017. E-mail: nglim@cmc.cuk.ac.kr

We thank Y.H. Choi and S.K. Kang (Industrial Safety and Health Research Institute), and J.W. Lee (Department of Internal Medicine, St. Mary's Hospital) for their professional and technical support.

Received 1 June 1999; accepted 9 July 1999.

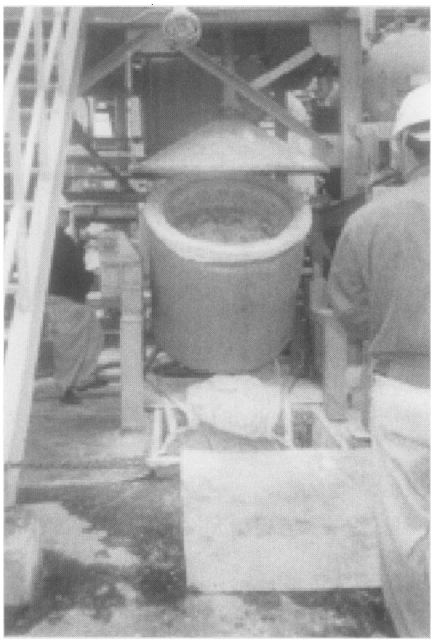

Figure 1. Demonstration of draining lime from a drainage tank after the deactivation process.

occupational benzene standard from 10 ppm to 1 ppm on the basis of qualitative and quantitative risk assessments of leukemia (*7*). However, the cause–effect relationship of low-level benzene exposure is under considerable debate because the studies of risk assessment depend not only on an assumption of a particular carcinogenic model but also on dose–response information from epidemiologic studies. Also, the studies did not successfully demonstrate excess risk at particular concentrations; the reduction of current standards is still in dispute worldwide. The 8-hr-TWA exposure standard is 10 ppm (e.g., Belgium, Denmark, Finland, Japan, Korea, and the Netherlands) or 5 ppm (e.g., Germany and the United Kingdom) in many countries (*8*).

Etiologies of aplastic anemia. Aplastic anemia can be caused by both hereditary and acquired factors. Drugs, viruses, organic compounds, and radiation are implicated causes of the acquired form. Fanconi anemia is a well-known inherited abnormality that causes the disease. At least five different genetic defects may induce Fanconi anemia, and one variant has a mutation of the *FACC* gene, which is involved in the cellular response to DNA damage (*9*).

Aplastic anemia may be acquired from the use of drugs (e.g., antimetabolites, antitumor agents, gold, chloramphenicol, phenylbutazone, sulfonamides); radiation; chemicals (e.g., benzene, solvents, insecticides); viruses (e.g., non-A, non-B, non-C hepatitis virus, human immunodeficiency virus, Epstein-Barr virus); paroxysmal nocturnal hemoglobinuria; pregnancy; connective tissue disorders; and graft versus host disease. Hereditary causes of aplastic anemia are Fanconi anemia, dyskeratosis congenita, and Schwachman syndrome.

Fifty percent of cases are idiopathic, and even for patients for whom a well-defined association between exposure and subsequent development of aplastic anemia has been established, it remains unclear why only a small proportion of those exposed to a given agent develop the disease.

Hematotoxicity and carcinogenecity. In acquired aplastic anemia, the disease results from two main pathogenic mechanisms: an acquired intrinsic stem cell defect and an immunosuppressive mechanism (*9*). Benzene itself is not myelotoxic or mutagenic. It is principally metabolized in the liver, and the metabolites are transported to the bone marrow and other organs. The active metabolites of benzene exert direct toxicity and alter differentiation patterns in the bone marrow. The immunosuppressive function of benzene is keeping with its lymphocytotoxic effect (*2*).

The carcinogenic mechanism of benzene is different from that of other chemicals. Some carcinogens, such as benzopyrene, aromatic amines, and aflatoxin, are thought to be activated to a single, ultimate carcinogenic metabolite, which is highly electrophilic; these carcinogens are also thought to bind strongly to DNA in a covalent fashion (*10*). Benzene is thought to be carcinogenic because of the combined effects of its metabolites (e.g., hydroquinone, *p*-benzoquinone, 1,2,4-benzenetriol); the potential mechanism involves these metabolites binding to DNA and causing oxidative stress (*11*). These active metabolites are involved in the causation of chromosome damage such as strand breaks, hyperploidy, and deletions in humans and animal species exposed to benzene. These chromosomal aberrations may lead to the inactivation of *p53* or other tumor-suppressor genes, and these events may be involved in leukemogenesis (*7*).

Table 1. Blood test results.

Date	RBC (no./mm^3)	Hemoglobin (g/dL)	Hematocrit (%)	WBC (no./mm^3)
5 October 1993 (yearly health exam)	4.95×10^6	15.0	44	6,600
27 April 1998 (yearly health exam)	4.85×10^6	15.1	44	6,400
5 November 1998 (aplastic anemia)	2.52×10^6	8.3	25	2,600
26 February 1999 (follow-up exam)	1.95×10^6	6.3	17.9	2,200

Abbreviations: RBC, red blood cells; WBC, white blood cells.

The data regarding benzene-induced clastogenesis in hematopoietic cells are not conclusive, however (*6*). Some investigators indicated that numerical or structural chromosomal aberrations were increased in workers who had long-term exposure to benzene; the ratios were increased in leukemia that occurred after benzene exposure. Others were not able to show any significant differences between the exposed and control groups (*12*).

Pancytopenia and aplastic anemia are not distinct diseases, but rather a continuum of changes reflecting the severity of bone marrow damage. Further, Aksoy and Erdem (*3*) reported the progression of aplastic anemia in a benzene-exposed individual through a preleukemic phase into frank acute leukemia. These findings were observed with high-level benzene exposure and not with low-level exposure.

Chemical, medical, or toxic substances may cause aplastic anemia in a dose-dependent or idiosyncratic way. To date, there is no evidence that low-level benzene exposure induces aplastic anemia through an idiosyncratic mechanism (*13*). However, benzene metabolism is quantitatively different at different dose levels. A relatively higher proportion of benzene is converted to toxic metabolites at low doses, suggesting that linear extrapolation of risk from high-dose studies may underestimate the true risk of low-dose benzene exposure (*7*).

Risk assessment. The establishment of benzene toxicity and setting of current standards has been primarily because of epidemiologic studies. Most investigators base risk predictions for exposures on rubber workers who were exposed to high concentrations of benzene; an exposure–response analysis by Rabbe and Wong (*14*) indicated that there was no increase of acute myeloid leukemia (AML) for cumulative exposure < 200 ppm-years. The exposure levels of petroleum industry workers are generally < 1 ppm on an 8-hr TWA basis, and the excess cases of leukemia were inconsistently observed. Christie et al. (*15*) reported a significant excess of myeloid leukemia in Australian

Table 2. Concentrations of airborne benzene and urinary muconic acid resulting from environmental surveys of the patient's workplace (November 1998).

Workplace	Airborne benzene (ppm)	Urinary muconic acid (mg/L)
Deactivation process (personal sampling)	0.07–0.40	0.03–0.08
Packaging process (personal sampling)	0.00–0.04	0.03–0.18
Drainage tank (area sampling)	0.19–0.26	–
Packaging process (area sampling)	0.02	–

petroleum industry workers. Jakobsson et al. (*16*) also reported a significantly elevated risk of AML in male gasoline station attendants in Sweden, but in many other studies, no increased risk of AML was observed in petroleum workers (*14*). In a study of Canadian petroleum distribution workers, Schnatter et al. (*17*) examined leukemia risk by benzene exposure level and noted the possibility that long-term exposure, regardless of the concentration, can result in leukemia.

Recently, there have been increasing concerns about low-level benzene toxicity in communities and work areas because benzene is ubiquitous in the environment; a few case reports imply that < 0.1 ppm benzene, even for a short time, induced hematologic abnormalities. In 1994 Stern et al. (*18*) reported a case of aplastic anemia in an American soldier who fought in the Gulf War; the disease was attributed to a possible exposure to benzene in the toxic smoke produced by burning oil wells. The smoke contained 3.1–9.1 ng/m^3 polycyclic aromatic hydrocarbons. Molinini et al. (*19*) reported a case of aplastic anemia in a young coke plant worker who was exposed to low-level benzene for 3 years. In 1994 the Italian Toxicology Commission reported that 3–50 cases of leukemia out of 1,000 could be caused by benzene from motor vehicle exhaust (*19*).

Biomonitoring. Measurement of blood benzene concentrations and benzene in exhaled breath are good means of assessing exposure, but the timing of measurement is important because of the short half-life of benzene. Urinary phenol has traditionally been used to biomonitor benzene exposure because roughly one-fourth to one-half of administered benzene is metabolized to phenol. However, there are other sources of urinary phenol, including dietary intake (*20*). When exposures are to relatively low levels of benzene, the background level of phenol obscures the benzene exposure. The measurement of phenol can be used to determine if someone has been recently exposed to high levels of benzene, but it is not useful for screening in the workplace, particularly if the level of benzene is low. Urinary *S*-phenylmercapturic acid (S-PMA) and tt-MA are now used instead of phenol in biologic monitoring of benzene. Although the analytical sensitivity of the S-PMA assay is much higher than that of tt-MA, tt-MA is a more sensitive biomarker than S-PMA and the assay is easier to perform and is more readily available (*21*). Shortcomings of the tt-MA assay are that there are other sources of this urinary metabolite, such as metabolism of sorbic acid (a food additive), and that tt-MA has a relatively shorter urinary half-life than S-PMA (*22*). The mean postshift tt-MA concentrations corresponding to a benzene 8-hr TWA exposure of 0.5–1.0 ppm are 0.8–1.4 mg/g creatinine (*23*), and exposure to 5.0 ppm benzene resulted in 3–8 mg/L urine (*24*).

We measured urinary tt-MA of the coworkers of the patient in this case to assess benzene exposure. Airborne benzene concentrations were higher in the deactivation process than in the packaging process, but urinary tt-MA levels were higher in the packaging workers. The packaging process was an indoor process, and the workers packed the products continuously through the work day. In the outdoor deactivation process, however, the workers poured the lime into the tank and drained the tank after the reaction; exposure was intermittent and total exposure time was < 30 min. For the packaging workers, the longer exposure time in a relatively closed space seems to result in higher levels of urinary tt-MA.

Conclusion

The patient in this case was otherwise healthy, and there was no extraoccupational exposure to hematotoxic agents in his daily life (e.g., hobbies, medications, etc.). He had not lived near a nuclear power station. The serologic markers and history for viral infection was negative. The chromosomal study was normal, with no aberrations observed. Based on the environmental investigation of the patient's workplace, he was exposed to low-level benzene for 21 years while packaging the powder resin and pouring lime into the deactivation tank. We also suspect that he had been exposed to high-level benzene for a short time when he cleaned the reaction tank.

The toxicity of low-level benzene is not only an occupational problem; environmental exposures of the general population to benzene from car exhaust, cigarette smoking, and indoor air should also be of concern. More research is needed to establish the toxicity of low-level benzene.

Reference and Notes

1. Rugo HS, Damon LE. Occupational hematology. In: Occupational and Environmental Medicine (LaDou J, ed). 2nd ed. East Norwalk, CT:Appleton and Lange, 1997;204–220
2. Smith MT. Overview of benzene-induced aplastic anemia. Eur J Haematol 57:107–110 (1996).
3. Aksoy M, Erdem S. Followup study on the mortality and the development of leukemia in 44 pancytopenic patients with chronic exposure to benzene. Blood 52(2):285–292 (1978).
4. Rinsky RA, Smith JB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. Benzene and leukemia. An epidemiologic risk assessment. N Engl J Med 316:1044–1050 (1987).
5. Cha CW, Kim KJ, Kim JC. Development of technology for environmental assessment and biological monitoring of workers exposed to benzene. Korean J Occup Med 6:122–133 (1994).
6. Paustenbach DJ, Bass RD, Price P. Benzene toxicity and risk assessment, 1972–1992: implications for future regulation. Environ Health Perspect 101(suppl 6):177–200 (1993).
7. Landrigan PJ, Nicholson WJ. Benzene. In: Environmental and Occupational Medicine (Rom WN, ed). 3rd ed. Philadelphia, PA:Lippincott and Raven, 1998;1109–1113.
8. Worksafe Australia. Exposure Standard: Benzene. Sydney, Australia:National Occupational Health and Safety Administration. Available: http://www.worksafe.gov.au/worksafe/exp/az/benzene.htm [cited 30 April 1999].
9. Castro-Malaspina H, O'Reilly RJ. Aplastic anemia and myelodysplastic syndromes. In: Harrison's Principles of Internal Medicine (Fauci A. Braunwald E, Isselbacher J, Wilson D, Martin JB, Kasper DL, Hanson SL, Longo DL, eds). 14th ed. New York:McGraw-Hill, 1998;672–679.
10. Smith MT. The mechanism of benzene-induced leukemia: a hypothesis and speculations on the causes of leukemia. Environ Health Perspect 104(suppl 6):1219–1225 (1996).
11. Snyder R, Hedli CC. An overview of benzene metabolism. Environ Health Perspect 104(suppl 6):1165–1171 (1996).
12. Tunca BT, Egeli U. Cytogenetic findings on shoe workers exposed long-term to benzene. Environ Health Perspect 104(suppl 6):1313–1317 (1996).
13. Snyder R, Witz G, Goldstein BD. The toxicology of benzene. Environ Health Perspect 100:293–306 (1993).
14. Rabbe GK, Wong O. Leukemia mortality by cell type in petroleum workers with potential exposure to benzene. Environ Health Perspect 104(suppl 6):1381–1392 (1996).
15. Christie D, Robinson K, Gordon I, Bisby J. A prospective study in the Australian petroleum industry. II. Incidence of cancer. Br J Ind Med 48:511–514 (1991).
16. Jakobsson R, Ahlbom A, Bellander T, Lundberg I. Acute myeloid leukemia among petrol station attendants. Arch Environ Health 48(4):255–259 (1993).
17. Schnatter AR, Katz AM, Nicolich MJ, Thériault G. A retrospective mortality study among Canadian petroleum marketing and distribution workers. Environ Health Perspect 101(suppl 6):85–99 (1993).
18 Stern MA, Eckman J, Offerman MK. Aplastic anemia after exposure to burning oil [letter]. N Engl J Med 331:58 (1994).
19. Molinini R, Mera E, Pavone V, Liso V. Aplastic anemia in a young coke plant worker. Int Arch Occup Environ Health 69:144–146 (1997).
20. Bechtold WE, Lucier G, Birnbaum LS, Yin SN, Li GL, Henderson RF. Muconic acid determinations in urine as a biological exposure index for workers occupationally exposed to benzene. Am Ind Hyg Assoc J 52(11): 473–478 (1991).
21. Boogard PJ, van Sittert NJ. Suitability of *S*-Phenyl mercapturic acid and *trans-trans*-muconic acid as biomarkers for exposure to low concentrations of benzene. Environ Health Perspect 104(suppl 6):1151–1157 (1996).
22. Weisel C, Yu R, Roy A, Georgopoulos P. Biomarkers of environmental benzene exposure. Environ Health Perspect 104(suppl 6):1141–1146 (1996).
23. Lauwerys RR, Buchet JP, Andrien F. Muconic acid in urine: a reliable indicator of occupational exposure to benzene. Am J Ind Med 2:297–300 (1994).
24. Inoue O, Seiji K, Nakatsuka H, Watanabe T, Yin SN, Li GL, Cai SX, Jin C, Ikeda M. Urinary t,t-muconic acid as an indicator of exposure to benzene. Br J Ind Med 46:122–127 (1989).